

Remarks

Claims 6-10 and 33-45 are pending in the subject application. Applicants acknowledge that claims 33-39 and 45 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 1-5, 7, 11-39 and 44-45, amended claim 6. Support for the new claims can be found throughout the subject specification and in the claims as originally filed. Applicants respectfully submit that the amendments made to the claims do not raise new issues, require new consideration, raise a requirement for a new search, or introduce new matter as the amendments are being made to conform with the restriction requirements previously issued in this matter (e.g., the election of topiramate (2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate in the Election of February 12, 2003). Thus, the claims have been amended to reflect the election of topiramate (2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate) in the claimed methods of promoting wound healing. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 6, 8-10 and 40-43 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

In the last Office Action, claims 6-10 and 40-43 were rejected under judicially created doctrine as being drawn to an improper Markush group. It was asserted a common nucleus is absent among the various compounds encompassed in instant Formula I when X_1 is CH_2 or oxygen in a ring to which methylenedioxy groups may optionally be fused. Applicants respectfully submit that this issue is now moot in view of the amendment made to the claims (namely, the amendment of the independent claim to provide a recitation of topiramate (2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate) and the cancellation of claim 7 in which the compounds of Formula I were provided). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-10 were rejected in the last Office Action under 35 U.S.C. § 103 as being unpatentable over Blake *et al.*, WO 00/10610. The Office Action argues that claim 1 is not limited to topical administration and that motivation to administer topiramate to promote wound healing flows from both the discussion on pages 4-14 of Blake's teaching clearly directed to wound healing and also the inclusion of the known anti-epileptic agent topiramate.

As the Patent Office is aware, three basic criteria must be met to establish a *prima facie* case

of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991). See M.P.E.P § 2143.

The teachings of Blake are directed to the production and use of bio-reductive conjugates of known therapeutic agents for use in targeting therapeutic agents to localized regions of hypoxic and/or ischemic tissue within the body (Blake *et al.* at page 1, paragraph 1). As is clear from the claims of Blake *et al.*, therapeutic agents, such as topiramate, are claimed “for use in the treatment of epilepsy” (see claims 22-23), not for the healing of wounds (claims 2-21). There is no teaching or suggestion in the claims or the specification of Blake *et al.* that topiramate is to be administered (topically or otherwise) for the promotion of wound healing. Additionally, it is respectfully submitted that where the reference addresses or claims medicaments for “use in the healing of wounds or the treatment of fibrotic disorders”, the therapeutic agents are limited to growth factor neutralizing agents or agents specific against only fibrotic growth factors (see claims 2 and 3). Specific examples of such agents are TGF- β 1; TGF- β 2; PDGF; IFN γ ; IL-1; TGF- β 3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN- γ , at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of: IFN- γ or activin and/or inhibin; agents that modulate actin assembly and organization, latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system (see claims 4-21). Notably absent from the listing of agents for use in the healing of wounds or the treatment of fibrotic disorders is topiramate and it is respectfully submitted that one skilled in the art would not have been motivated to use bio-reductive conjugates of topiramate for promoting wound healing in view of the teachings of Blake *et al.*

Turning to the teachings of the specification of Blake *et al.*, specification indicates that “the present invention extends the range of conditions to which the drug conjugates of the aforementioned PCT application may be applied to include the healing of wounds, and the treatment of fibrotic disorders, ulcerative colitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury,

cerebral reperfusion injury, hypertension, cystic fibrosis, psoriasis, para-psoriasis, peptic ulcers, gastric ulcers, duodenal ulcers, diabetic ulcers, dementia, oncology and AIDS” (page 4, paragraph 3). The specification then proceeds to provide subsections devoted to these classes of diseases or disorders that include the various therapeutic agents that can be used to treat the specified disease or disorder.

As indicated *supra*, the sections pointed to in the Office Action (pages 4-14) are solely directed to the use of bio-reductive conjugates of therapeutic agents such as TGF- β 1; TGF- β 2; PDGF; IFN γ ; IL-1; TGF- β 3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN- γ , at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of IFN- γ or activin and/or inhibin; agents that modulate actin assembly and organization; latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system for use in the healing of wounds. With respect to bio-reductive conjugates of topiramate, it is respectfully submitted that the specification explicitly states, on page 15:

1.3. Epilepsy

The therapeutic agent for use in the treatment of epilepsy may for example be Phenytoin, Phenobarbitone, Sodium Valporate, Topiramite.
(misspelling in original)

Applicants respectfully submit that one skilled in the art, based on the claims and teachings of the specification would not, and could not, reasonably infer that the reference teaches, suggests, or motivates one skilled in the relevant art to use topiramate for promoting wound healing and that the claimed invention is not rendered obvious by the cited reference.

Applicants further submit that there would have been no motivation to use topiramate for use in wound healing because such a pharmacological activity for topiramate was not recognized in the art prior to the time of instant invention. As the Patent Office may be aware, topiramate is indicated for use as an anti-convulsant (anti-epileptic) agent for patients with partial onset seizures. As there is no teaching or suggestion in any prior art of record that one of the benefits of topiramate included promoting wound healing; accordingly, it is respectfully submitted that one skilled in the art would not have been motivated to use topiramate in methods of promoting wound healing and reconsideration and withdrawal of the rejection is respectfully requested.

In further support of this position, Applicants submit the declarations of Drs. Gregory Schultz and David Mozingo, individuals skilled in the art of wound healing. Drs. Schultz and Mozingo have reviewed the Office Actions, and the responses filed on behalf of the Applicants thereto, the specification of the subject patent application and the prior art cited in the Office Actions. As indicated in the declarations, these individuals would not have been motivated to utilize bioreductive conjugates of topiramate for promoting wound healing in view of the teachings of Blake *et al.* nor would the teachings of Blake *et al.* have suggested the use of topiramate in promoting wound healing. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicants also respectfully submit that a *prima facie* case of obviousness with respect to the claimed invention has not been raised in this matter as one skilled in the relevant art would not have had a reasonable expectation of success in practicing the invention as currently claimed. As indicated *supra*, there was no recognition in the art that topiramate had a pharmacologic activity that promoted wound healing; thus one skilled in the art would not have had a reasonable expectation of success in promoting wound healing via the administration of a composition containing topiramate to an individual. In further support of this position, Applicants respectfully submit the declarations of Drs. Schultz and Mozingo. As indicated in these declarations (at paragraph 2) these individuals would not have expected topiramate to provide therapeutic benefit for promoting wound healing when administered to individuals. Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established with respect to the claimed invention and reconsideration and withdrawal of the rejections is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Declarations of Drs. Gregory Schultz and David Mozingo with Curriculum Vitae
Copy of Physician's Desk Reference (2000) pp.2209-2216